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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/878,348	06/18/97	HEATH	A 2257-1-001

EXAMINER

HM12/0303

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ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 03/03/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 8/9/99; 1/27/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-10, 12, 13, 15-23 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-10, 12, 13, 15-23 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's after final amendment, filed 8/9/00 (Paper No. 11), has been entered. Claims 1 and 4 were amended.

Applicant's after final amendment, filed 1/29/00 (Paper No. 14), is acknowledged.

Claims 1-10, 12, 13, 15-23 are pending and under consideration.
Claims 11 and 14 have been canceled previously.

2. Upon reconsideration of an updated search, the following New Grounds Of Rejection have been set forth herein.
Applicant's arguments of record are rendered moot in view of these New Grounds of Rejection.

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 6.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes, if necessary.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Although the previous Advisory Action (Paper No. 12) indicated that the previous rejections under 35 USC 112, first and second, paragraphs have been withdrawn; it is noted that applicant's after final amendment, filed 8/9/99, which was entered, did not amend the claimed immunogenic composition to comprise anti-CD40 antibodies and CD40 ligand. Therefore, the following scope rejection applies.

Claims 15-23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "antibodies that bind CD40 or CD40L" as the "adjuvant adapted to stimulate B lymphocyte CD40", does not reasonably provide enablement for any such "adjuvant" essentially for the reasons set forth in Paper Nos. 6/9.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies adjuvants other anti-CD40 antibodies or CD40L that are adapted to stimulate B cells via CD40. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any POLYPEPTIDE other than those defined by SEQ ID NO.

As indicated previously, it was noted the specification discloses that the instant adjuvant includes references to any string of amino acids or ligand which is selected so as to bind to at least a part of CD40 (page 8, paragraph 1). There is insufficient direction and guidance as to how to use any such "string of amino acids". Further for the reasons of record; it is not sufficient to simply bind to at least a part of CD40 to provide for adjuvant properties, as encompassed by the claimed invention. For example, there are both agonistic and antagonistic CD40-specific antibodies and agonistic antibodies need to be cross-linked in some manner to provide augmentation of the immune response and lymphocyte signaling.

With respect to the CD40 ligand, Armitage et al. (U.S. Patent No. 5,961,974) discloses that membrane bound CD40L and oligomeric CD40L (dimeric or trimeric) are useful as CD40 agonists, while monomeric CD40L is useful as a CD40 antagonist (see entire document). There appears insufficient guidance and enablement for the use of adjuvants comprising CD40 ligand, wherein the CD40L is not at least oligomeric and preferably trimeric. Mazzei et al. (J. Biol. Chem. 270: 7025, 1995; of record); the trimeric conformation of the CD40 ligand may be required for binding to CD40 and its ability to stimulate via CD40 that is indistinguishable from the membrane bound from of the protein (see entire document, including Abstract and Discussion). While functional soluble forms of recombinant CD40L have been produced, it was known at the time the invention was made that a CD40L-IgG1-Fc fusion proteins which exists as a disulphide-linked dimer has low activity on B cells and required additional cytokines for B cell proliferation under defined culture conditions.

Therefore it would be expected that any adjuvant capable of stimulating B cell via CD40, including "parts" of CD40L would not result in sufficient signaling associated with the claimed adjuvants. There appears insufficient guidance and direction as to enablement of the claimed "adjuvants adapted to stimulate B cells via CD40,, commensurate in scope with the claimed invention. Applicant has not enabled such adjuvants with CD40L or antibodies that bind CD40 that do not have the appropriate conformation or sufficient multivalency to stimulate lymphocyte responses, associated with the properties of an adjuvant.

It was known at the time the invention was made that sufficient stimulation via CD40 required cross-linking of CD40 via CD40-specific antibodies or CD40 ligand in combination with appropriate lymphokines. In applying CD40 ligand, cross-linking occurred via transfected or surface-bound CD40 ligand. There is insufficient guidance and direction to enable adjuvants adapted to stimulate a B lymphocyte cell surface receptor CD40 and the production of said adjuvants other than providing CD40 ligand as oligomers and particularly trimers or polypeptides having the appropriate multivalency or providing CD40-specific antibodies in a manner that induces appropriate immune responses in vivo.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective adjuvants, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and methods and absent working examples providing evidence which is reasonably predictive that the claimed compositions and methods are effective as an adjuvant.

The amendments must be supported by the specification so as not to add any new matter.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 8-10, 12, 13, 15, 16 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mond et al. (U.S. Patent No. 5,874,085) (see entire document).

Mond et al. teach the production and use of multivalent vaccines which comprise CD40L and antigens to stimulate B cell responses to a variety of T cell dependent and independent antigens, including protein/polysaccharide/soluble antigens (for example, see Background of the Invention, Summary of the Invention, Detailed Description of the Invention and Claims).

The recitation of a process limitation such as fusion protein is not seen as further limiting the claimed products, as it is presumed that equivalent products can be obtained by multiple routes. It is noted that the reference teaches a variety of means to cross-link adjuvants or activators such as CD40L to antigens of interest and the reference teaches producing the adjuvants such as CD40L recombinantly. Therefore, the prior art reads on the claimed immunogenic compositions, including fusion proteins. Also, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced vaccine formulations comprising CD40L and a variety of antigens and methods of preparing the same. The burden is on the applicant to establish a patentable distinction between the claimed and referenced immunogenic compositions and methods of making the same.

9. Claims 1-4, 8-10, 12, 13, 15, 16 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mond et al. (U.S. Patent No. 5,932,427) (see entire document).

Mond et al. teach the production and use of multivalent vaccines which comprise CD40L (for example, see column 8, lines 60-65; column 11, lines 4-8; and Examples 2/7) and antigens to stimulate B cell responses to a variety of T cell dependent and independent antigens, including protein/polysaccharide/soluble antigens (for example, see Background of the Invention, Summary of the Invention, Detailed Description of the Invention and Claims).

The recitation of a process limitation such as fusion protein is not seen as further limiting the claimed products, as it is presumed that equivalent products can be obtained by multiple routes. It is noted that the reference teaches a variety of means to cross-link adjuvants or activators such as CD40L to antigens of interest and the reference teaches producing the adjuvants recombinantly. Therefore, the prior art reads on the claimed immunogenic compositions, including fusion proteins. Also, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced vaccine formulations comprising CD40L and a variety of antigens and methods of preparing the same. The burden is on the applicant to establish a patentable distinction between the claimed and referenced immunogenic compositions and methods of making the same.

10. Claims 1-10, 12, 13 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mond et al. (U.S. Patent No. 5,874,085) AND Mond et al. (U.S. Patent No. 5,932,427) in view of Ledbetter et al.(U.S. Patent No. 5,247,069) and Armitage et al. (U.S. Patent No. 5,961,974) and in view of the art known methods of making and providing vaccine formulations to various antigens at the time the invention was made, as acknowledged by applicant in their traverse response to the restriction requirement, filed 2/27/98 (Paper No. 5), as acknowledged by applicant's specification where it is stated that "it should be apparent to those skilled in the art that this methodology may also be applied to any antigens" (page 7, lines 1-2) .

Both Mond et al. references are taught above.

Mond et al. differ from the claimed invention by not disclosing the use of anti-CD40 antibodies as adjuvants in the immunogenic compositions and the production of the immunogenic composition as a fusion protein per se.

Ledbetter et al. teaches the use of Bp50-specific antibodies as adjuvants (see entire document, particularly Summary of the Invention, and Section 5.4.1 It was known at the time the invention was made that the Bp50-specific antibodies taught by Ledbetter et al. were specific for CD40, that is, Bp50 and CD40 are the same antigen specificity.

Armitage et al. teach that oligomeric CD40L and cross-linked anti-CD40 antibodies are agonistic and that CD40 agonistic were useful as vaccine adjuvants (see entire document, including columns 9-10).

It would have been obvious to the ordinary artisan at the time the invention was made to provide the elements of the immunogenic composition or the fused construct itself in a convenient homogeneous form, such as providing the anti-CD40 antibodies in various recombinant forms (e.g. monoclonal or humanized antibodies) or as fusion proteins.

Further and as noted above and of record, both applicant's response to the restriction requirement and the specification as filed indicate that vaccine formulations and methods of making said vaccines comprising an adjuvant, as encompassed by the dependent claims were all well known and practiced by the ordinary artisan at the time the invention was made.

Therefore, the kits comprising cells and nucleic acids encoding the immunogenic compositions, including the fusion proteins comprising the CD40L/anti-CD40 antibody and antigen of interest were obvious at the time the invention was made, as a known and convenient means to produce said compositions.

One of ordinary skill in the art at the time the invention was made would have been motivated to make and to provide immunogenic compositions with various T-dependent/T-independent antigens with the stimulatory or adjuvant properties of CD40L or anti-CD40 antibodies to generate immune response to a variety of antigens at the time the invention was made, including providing these elements joined together in various formulations or constructs, as taught and known by the prior art. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
Patent Examiner
Technology Center 1600
March 2, 2000

PENDING CLAIMS

1. (Twice Amended) An immunogenic composition comprising an adjuvant and an antigen; wherein said adjuvant and said antigen are joined together; wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand; and

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell.

2. (Amended) A vaccine including the immunogenic composition according to Claim 1.

3. (Amended) A vaccine according to Claim 2 wherein said antigen is a T-cell dependent or T-cell independent antigen, or part of said T-cell dependent or T-cell independent antigen.

4. (Amended) A vaccine according to Claim 2 wherein said adjuvant is a CD40 ligand.

5. (Amended) A vaccine according to Claim 2 wherein said adjuvant is an antibody raised against said CD40, or a part of said antibody that is effective at binding CD40.

6. A vaccine according to Claim 5 wherein the antibody is monoclonal.

7. A vaccine according to Claim 5 wherein the antibody is humanised.

8. A vaccine according to Claim 3 wherein said antigen is soluble.

9. A vaccine according to Claim 3 wherein said antigen is a protein.

10. A vaccine A method wherein said antigen is a polysaccharide.

12. (Amended) A vaccine according to Claim 3 wherein said antigen is a protein or part thereof, and said antigen is fused to said adjuvant so as to provide a fusion protein.

13. (Amended) A vaccine according to Claim 2 further comprising at least one cytokine.

15. (Amended) A method for the manufacture of a vaccine capable of enhancing immunity comprising

(a) selecting a suitable T-cell dependent and/or T-cell independent antigen, or parts thereof, and

(b) associating or combining said antigen with an adjuvant; wherein said adjuvant is adapted to stimulate B-lymphocyte receptor, CD40.